Remarks

Favorable reconsideration of this application is respectfully requested. Claim 1 has been amended. No new matter has been added. Claims 1-7 have been examined. Claims 8-10 are considered withdrawn from consideration. Claims 1-10 are pending.

Claim Rejections- 35 U.S.C. §112

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement.

The term "prevention" has been removed from claim 1. Applicants respectfully submit that the claims are enabled, and request that the rejection be withdrawn.

Claim Rejections- 35 U.S.C. §103

Claims 1 and 3-7 are rejected under 35 USC 103 (a) as being unpatentable over Kobori et al. (Cell Death and Differentiation, Oct. 3, 2003, published online, Vol. II, pgs. 123-1 30). Claims 1-7 also are rejected under 35 USC 103 (a) as being unpatentable over Yuan et al. (U.S. 6,552,071 B2) in view of Matsui et al. (Exp. Opin. Theur. Targets, 2003, Vol. 7, No. 6, pgs. 701 -724). Applicants respectfully traverse these rejections for at least the following reasons.

On page 8, the rejection states that Kobori et al teaches that, the ability of wedelolactone to inhibit the activation of NF-kB pathway provides an interesting potential lead compound in anti-inflammatory therapy to inhibit diseases such as rheumatoid arthritis. (See pg. 128, right col, the last sentence of paragraph 2).

On page 9, the rejection over Kobori et al. states that Kobori et al. however do teach that wedelolactone which comes from the extract of E. *prostrata* L. is a potential compound in the treatment of anti-inflammatory diseases including rheumatoid arthritis. Moreover, Kobori et al. teach that the aforementioned compound can be extracted from the entire plant, filtered, concentrated, and washed with hot water which necessarily reads on applicant's claim limitation of water temperature of 50-80 °C. While Kobori et al. is silent on elution of the precipitate using petroleum ether/acetone mixture,

dichloromethane/acetone mixture, or a tolueneacetone-formate mixture, the rejection states that the resulting precipitate of the prior art is substantially the same as that of applicant regardless of the type of elution solvents utilized. Consequently, a prima facie case of obviousness has been established." Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the wedelolactone compound of Kobori et al. to treat rheumatoid arthritis since Kobori et al. teach that wedelolactone is a potential compound in the treatment of anti-inflammatory disease including rheumatoid arthritis. Given the teachings of Kobori et al., one of ordinary skill would have been motivated to utilize the compound of Kobori et al. to treat rheumatoid arthritis as taught by Kobori et al. with the reasonable expectation of providing a method that is efficient in treating rheumatoid arthritis and other inflammatory diseases. Therefore, Claims 1 and 3-7 are rejected.

On page 10, the rejection over Yuan et al. in view of Matsui et al states that Yuan et al. teach methods and compounds for treating inflammation (see abstract and col. 1, lines 13-15). The methods involve the use of the plant extract wedelolactone or comprise administering wedelolactone or a salt thereof to a subject (see col. 1, lines 43-46 and 55-62). Particularly, Yuan et al. teach a method of treating inflammation in a subject.

On page 12, the rejection further states that Matsui et al. teach that rheumatoid arthritis (RA) is a common chronic inflammatory joint disease with destruction of the cartilage and bone. RA is characterized by the intensively proliferating synoviocytes and the dense infiltration of various types of activated immune competent cells (see pg. 708, left col.). Matsui et al. further teach that RA patients possess aberrant I cells which react with collagen type II autoantigens which have been found to induce inflammatory arthritis in mice (see pg. 709, left col., paragraph 1). Importantly, Matsui et al. teach that cytokines and chemokines are involved in the development of RA and that RA patients tend to show an increase in pro-inflammatory cytokines (see pg. 709, left col., paragraph 2).

However, Applicants respectfully disagree with the above interpretations and conclusions for at least the following reasons.

1. Autoimmune arthritis is a disease different from other inflammatory diseases.

There are various types of inflammatory diseases and the different types of inflammatory diseases have significantly different mechanisms. It is well known that common inflammatory diseases are simply infections caused by microorganisms such as bacteria and viruses, where corresponding pathological reactions are characterized with the increase of leukocyte number and neutrophilic granulocyte. Such inflammatory diseases are usually referred to as acute inflammatory disease, where treatment typically has been through the use of antibiotics. Inflammatory diseases, other than the infective acute inflammatory diseases, also include non-specific inflammatory diseases. Non-specific inflammatory diseases are known as immune inflammation, which is an iterative and chronic process caused through a condition of the immune system.

Applicants respectfully submit that autoimmune arthritis as recited by claim 1, including for example RA, occurs through a mechanism such as follows. When an antigen enters into the human body, it is taken up by macrophages. After digestion and concentration, the antigen combines with HLA-DR molecule to form a complex. If such complex is recognized by the receptor on the T-cell, the T lymphocyte is activated and cause a series of immunity reactions including activation of B lymphocyte which is then differentiated into plasmocyte. The plasmocytes excrete a lot of immunoglobin including RA factors which are antibodies against the Fc fragment of IgG. Since RA factors bind to the corresponding IgG, they are autologous antibodies. The complexes formed by RA factors and IgGs and various cytokines can cause pathological changes inside of and outside of the joint, which can result in autoimmune arthritis. (See e.g. page 1, lines 20-36 of Applicants' disclosure).

Summing up, the immune inflammatory diseases of arthritis are completely different from other inflammatory diseases.

However, none of the references Kobori et al., Yuan et al., and Matsui et al. disclose or suggest that wedelolactone can be used to effectively treat *in vivo* the specific immune inflammatory disease of claim 1, namely autoimmune arthritis.

2. Kobori et al. is insufficient to provide an expectation of success that would lead one of skill in the art to the claimed invention.

Kobori et al. discusses that wedelolactone has anti-inflammatory effect through the specific inhibition of IKK activity and caspase-11 expression. However, Kobori et al. only reports on the activity of wedelolactone to specifically inhibit the activation of NF-κB and inhibit the overexpression of Caspase-11 induced by LPS. Thus, Kobori et al have only tested the activity of wedelolactone, on the cell level, for a specific mechanism that is different from autoimmune arthritis discussed above. While Kobori et al. contemplates that their pathological mechanism might apply in treatments relating to cell death and inflammatory diseases in general, it is well-known that a disease is usually caused by several factors and is unpredictable. In other words, one disease may involve several pathways or factors. Therefore, it is quite common that even if one compound is effective in inhibiting one pathway, it is uncertain whether it is effective in inhibiting others. Moreover, *in vivo* and *in vitro* environments are different. That is, a compound which may be effective for *in vitro* experiments, however, may be inactive for *in vivo* applications, for example due to low bioavailability and distribution in tissues. The experiments of Kobori et al. are all on the cell level, and Kobori et al. provides no *in vivo* experiments to show treatment effects of wedelolactone on any inflammatory diseases, much less any treatment effects on immune inflammatory diseases.

Thus, Kobori et al. merely discusses that, *in vitro,* wedelolactone can specifically inhibit the activation of NF-κB and inhibit the overexpression of Caspase-11 induced by LPS, which is an entirely different mechanism. However, there is no reasonable expectation of success that one of skill in the art would arrive at the claimed invention, where wedelolactone is effective in treating autoimmune arthritis.

Moreover, although Kobori et al mentions that "[t]he ability of wedelolactone to inhibit the activation of NF-KB pathway provides an interesting prospective for using this compound as a potential lead compound in anti-inflammatory therapy to inhibit IL-1β levels in diseases such as rheumatoid arthritis, asthma and septic shock", the art of record clearly shows that around the time of Applicants' invention, wedelolactone has not been successfully used to treat rheumatoid arthritis, asthma, or septic shock. Consequently, claim 1 does not follow from Kobori et al.

3. Compounds such as antibiotics, which have been reported as being effective in treating common inflammation, have been widely shown to be ineffective in treating immune inflammation.

Kobori et al simply presents guesswork that inhibition of IL-1β levels is desired for treating RA. On the other hand, Matsui et al. reports that IL-18 plays an important role in RA. IL-1β is obviously not IL-18. Therefore, the state of the art is clearly hypothetical, and although compounds such as antibiotics can be used to treat common inflammation, there is no suggestion that they would be effective in treating immune inflammation such as RA.

Therefore, even if one of skill in the art reads Kobori et al., or the combination of Yuan et al. and Matsui et al., Applicants respectfully submit that claim 1 is non-obvious as there is no expectation of success in the art of record, at least because (1) the fact that a compound can inhibit one pathway or inhibit certain cytokines does not mean such compound is effective in treating immune inflammation such as RA; (2) it is commonly known that compounds, such as antibiotics, which are effective in treating common inflammation, have not translated to effective treatment of immune inflammation; and (3) without confirmed animal experimental data, it is very difficult to predict whether a compound is effective to treat treating immune inflammation such as RA. Consequently, claim 1 does not follow from the references cited, as without the benefit of Applicants' disclosure, there is no reasonable expectation of success that one of skill in the art would arrive at the claimed invention or achieve such benefits that it may enjoy.

Favorable reconsideration and withdrawal of the rejections are respectfully requested.

In view of the above amendments and remarks, Applicants respectfully request favorable reconsideration of this application in the form of a Notice of Allowance. If any questions arise regarding this communication, the Examiner is invited to contact Applicants' representative listed below.

Respectfully submitted,

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